In regulated chemicals, safe exposure limits are set based on in vivo studies of single chemicals administered at high doses to experimental animals and identification of the no-observed-adverse-effect-level (NOAEL). Though this is a practical and globally used approach, the vast majority of human real-life exposure scenarios have two main key components: low doses and many chemicals. In pharmacology and animal testing dose is quite clear and in most of the cases known. The creation of large toxicological databases and advances in machine-learning techniques have empowered computational approaches in toxicology. Work with these large databases based on regulatory data has allowed reproducibility assessment of animal models, which highlight weaknesses in traditional in vivo methods. This should lower the bars for the introduction of new approaches and represents a benchmark that is achievable for any alternative method validated against these methods. As to human toxicology the situation is different: the same persons might have been exposed to multitude of chemicals through the diet, environmental sources, use of consumer products or at the workplace (occupational exposure) and many times at the same time or sequentially. This makes exposure assessment even more complicated and hard to identify its linkage with long-term adverse health effects. Regulatory toxicology has somehow avoided to make decisions on the most common situations where human beings are daily. Even newly developed approaches such as grouping of chemicals for cumulative risk assessment are not considering real-life exposure scenarios as they are based on regulatory toxicology studies. There is a need for a paradigm shift of the current approaches for risk assessment towards a Real-Life Risk Simulation (RLRS) approach. There is no reason to believe today that the Exposure Limits on potentially toxic stimuli that have been set by the regulatory agencies are fully protective against serious adverse health effects in all real life exposure scenarios. The conclusion is applicable to essentially all potential contributing factors to disease amenable to Exposure Limits, including not only chemicals but other exposures, too. There is a need to encourage scientists to expand their mental capacity for more complicated evaluations and to face real life challenges.